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Evaluation of Medication Safety in the Discharge Medication of 509 Surgical Inpatients Using Electronic Prescription Support Software and an Extended Operational Interaction Classification

Inaugural-Dissertation

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Index of Contents

1. SUMMARY

Purpose We aimed to study drug interactions and dose adjustments for renal impairment in the discharge medication of surgical inpatients, and to evaluate strengths and limitations of Clinical Decision Support software (CDSS) for this task.

Methods Cross-sectional study in 509 surgical patients of a primary care hospital. We developed a customized interface for the CDSS MediQ, which we used for automated retrospective identification of drug interactions in the patients' discharge medication. Clinical relevance of interactions was evaluated based on the Zurich Interaction System (ZHIAS) that incorporates the Operational Classification of Drug Interactions (ORCA). Prescriptions were further analyzed for recommended dose adjustments in patients with a GFR <60 ml/min.

Results In 509 patients with 2,729 prescriptions MediQ generated 2,558 interaction alerts and 1,849 comments. Among those there were 10 "high danger" and 551 "average danger" alerts that we reclassified according to ORCA criteria. This resulted in 10 contraindicated combinations, 77 provisionally contraindicated combinations, 310 with a conditional and 164 with a minimal risk of adverse outcomes. The ZHIAS classification also provides categorical information on expected adverse outcomes and management recommendations, which are presented in detail. We identified 56 prescriptions without recommended dose adjustment for impaired renal function.

Conclusions CDSS identified a large number of drug interactions in surgical discharge medication, but according to ZHIAS criteria only a minor fraction appears to involve a substantial risk. CDSS should aim at reducing over-alerting and improve usability in order to become more efficacious regarding the prevention of adverse drug events in clinical practice.

2. INTRODUCTION

Drug interactions and resulting adverse drug events (ADE) are important challenges for pharmacotherapy. They cause considerable morbidity, mortality and costs, and have been estimated to be responsible for 1% of all hospital admissions [1-5]. Computerized physician order entry (CPOE) combined with clinical decision support software (CDSS) has been proposed as a valuable tool to prevent critical interactions and also to guide dose adjustment in patients with impaired renal function. On the one hand, several studies presented encouraging results [6, 7]. For example, one study was able to demonstrate a significant 81% reduction in medication errors after the introduction of CPOE with CDSS [8]. But on the other hand, several more recent studies concluded that commonly used CDSS suffer from "over-alerting", and that the resulting "alert-fatigue" among physicians is an important reason why they often fail to effectively improve medication safety in clinical practice [9-12]. Furthermore, the frequency of specific critical medication problems varies between different specialties and settings. New approaches may therefore first aim to analyze local safety issues with high efficiency, as this may subsequently support the development of targeted local measures in order to improve pharmacotherapy. In particular, we found that more data is needed for surgical inpatients in order to evaluate medication safety for this population. The current study therefore had two major aims. First, to describe and quantify medication safety with regard to drug interactions and renal dose adjustments in patients discharged from surgical care in a regional Swiss hospital using a new highly efficient CDSS interface for retrospective interaction analysis. Second, to improve the specificity of CDSS in identifying clinically relevant drug interactions and providing related practical prescribing information.

3. MATERIAL AND METHODS

Study design

We conducted a cross-sectional study in all surgical patients discharged between 1 January and 31 October 2009 from a primary care regional hospital, including patients from general surgery, orthopedics, urology, otorhinolaryngology and reconstructive surgery. There were no exclusion criteria except admissions for less than four nights; patients with a shorter stay were excluded in order to assure that pharmacotherapy was actively managed and well documented by the treating surgeons. The regional ethics committee had approved the study protocol including access to the hospital's clinical information system for study purposes. Pharmacotherapy at discharge, demographics, medical diagnoses and laboratory test results were retrospectively retrieved for each patient from their original medical records and the hospital's clinical information system, and data of all patients was stored in an anonymized master file. The latest available value for serum creatinine before discharge was used to estimate renal function according to the MDRD-GFR formula [13]. All drugs were then matched to their corresponding ATC codes, and single drugs that contained several active ingredients were split into their component substances and treated as separate prescriptions for all further analyses.

Subsequently we analyzed the data for the following outcomes of interest: 1. frequency and severity grading of drug interactions according to the commercially available CDSS MediQ; 2. extended classification and evaluation of the clinical relevance of interactions identified by MediQ according to the Zurich Interaction System (ZHIAS); 3. compliance with recommended dose adjustments in patients with an estimated GFR <60 ml/min based on MediQ alerts, Aronoff's *Drug Prescribing in Renal Failure* [14], and the manufacturers' national prescribing information (Arzneimittel-Kompendium der Schweiz). **Figure 1** shows an overview of the study procedures and global results.

MediQ and development of a customized interface for mass analysis

MediQ is a commercial CDSS for use as an Internet application (www.mediq.ch). The user manually enters concomitantly prescribed drugs for individual patients, and MediQ then identifies interactions and provides the following output. First, a four-level categorical severity grading that MediQ describes as: 3 = ”high” or “strong interaction”; 2 = ”average” or “clinically relevant interaction”; 1 = “low” or an interaction that is “relevant in exceptional cases”; 0 = “no interaction” or additional comments. This information is also presented in a matrix overview. Second, detailed free text information for each interaction. Third, additional tables that present pharmacokinetic effects on metabolizing enzymes and drug transporters as well as pharmacodynamic effects on the central nervous system for individual substances.
Because the manual entry of prescriptions for each patient would not be efficient for our purposes we developed, in collaboration with MediQ, a customized data interface for mass analysis. This allowed us to upload one structured text file over the Internet that contained an anonymous study number and the corresponding ATC codes of concomitantly prescribed drugs for each patient. Exactly the same analyses as for the usual Internet application were then executed on the MediQ server. The results could subsequently be downloaded over the Internet and imported into statistical software for further analyses. Because MediQ’s knowledge database is continuously updated it is of note that the interaction analyses presented in this study were all executed in July 2010.

ZHIAS classification

ZHIAS is an extended drug interaction classification system that was developed at our department during the conduct of this and other related studies. It features four major dimensions plus free text fields. The first dimension uses the well established and documented five-level grading according to the Operational Classification of Drug Interactions (ORCA) criteria [15]. Briefly, ORCA’s five operational levels are defined as follows: Grade 1 = “contraindicated combination”. The risk of such a combination always outweighs the benefit. Grade 2 = “provisionally contraindicated”. The combination should be

avoided unless interaction is desired or no alternative is available, monitoring may be necessary. Grade 3 = “conditional risk”. Monitoring or alternatives should be considered. Grade 4 = “minimal risk”. No special action is needed. Grade 5 = “no interaction”. ZHIAS’s other 3 major dimensions use dichotomous variables that relate to patient management, interaction mechanisms and adverse effects with an increased risk resulting from an interaction (see Table 4). For the current study an expert panel consisting of a surgeon (TF), two pharmacists (OZ and AF), and a clinical pharmacologist (SR) discussed the ZHIAS classifications of identified interactions until common agreement was achieved. For our assessments we referred to original and secondary literature, including but not limited to Hansten and Horn’s *Drug Interactions: analysis and management* [16], and *Stockley’s Drug Interactions* [17].

Data analysis

Data analysis was descriptive with presentation of results in text, tables and figures, and calculation of medians, means and proportions as appropriate. Data management and analyses were performed with STATA 11.1 for MacOS X (STATA corporation, College Station, TX, USA) and SPSS 19 for Windows (SPSS, Inc., Chicago, IL, USA).

4. RESULTS

Selection and characteristics of the study population

Demographic data of 552 consecutive surgical patients hospitalized for at least four nights at the Department of Surgery was retrieved from the hospital’s electronic information system. Thereafter the patients’ discharge medication was abstracted from their original medical records including discharge letters. Consequently, 43 patients were excluded because they had only one or no prescription. Characteristics of all remaining 509 included patients are presented in **Table 1**. Mean age was 60.4 years with a median and range of 70.5 (8 - 99)

years. The median number of concomitantly prescribed substances per patient was 5 (range 2 - 17), and **Table 1** also presents polypharmacy distribution over three broad categories. Frequency of prescriptions over drug classes is shown in **Table 2**. NSAIDs with paracetamol (acetaminophen) and metamizol (dipyrone) were the most commonly prescribed drug class, followed by antithrombotics and cardiovascular agents.

Identification and evaluation of drug interactions

Automated analysis using MediQ generated 2,558 interaction alerts and 1,849 additional comments (**Fig. 1**). As expected, the number of interaction alerts per patient markedly increased with a higher number of concomitantly prescribed substances (**Fig. 2**).

Table 3 presents results of the automated drug interaction analysis using MediQ along with our subsequent reclassification of MediQ “high” and “average” danger alerts according to ORCA criteria. Out of 10 combinations considered by MediQ as involving a “high danger” interaction none was classified as contraindicated and only one as provisionally contraindicated according to ORCA criteria; out of 551 prescriptions considered by MediQ as involving an “average danger” 10 were classified as contraindicated and 76 as provisionally contraindicated. The full evaluation of all MediQ high danger and average danger interaction alerts showing all ZHIAS dimensions is presented in **Table 4**. Evaluation regarding management of interactions according to ZHIAS concluded that 28.6% of provisionally contraindicated combinations and 21.9% of combinations with a conditional risk were most likely actually desired combinations with an acceptable risk-benefit ratio under the condition that patients are appropriately monitored. Nevertheless, at the same time in more than 70% there may exist alternative treatments with a possibly more favorable risk-benefit ratio. Regarding mechanisms, pharmacodynamic interactions were most frequent over all ORCA classes, and increased drug effects, particularly increased risk of bleeding, were the most frequently encountered potential adverse consequences resulting from interactions. Specific interacting combinations with the highest danger rating according to MediQ or ORCA are presented in **Table 5**. MediQ classified 6 specific combinations as “high danger”.

In these cases ORCA criteria emphasize that even if the potential adverse effect may be severe, all of these interactions could be managed with appropriate monitoring such as for hyperkalemia or QTc prolongations, followed by dose adjustment or stop of therapy if necessary. In contrast, those combinations with the highest ORCA rating may not necessarily be driven by a very high risk or severity of an adverse event: in eight out of ten cases the combined drugs have the same mechanism of action, and for two the weak evidence supporting ginkgo's efficacy led to our assessment of a generally unfavorable risk-benefit ratio. In addition, **Table 6** also presents all specific drug interactions classified by ZHIAS as ORCA 2 ("provisionally contraindicated"), and the 10 most frequent classified as ORCA 3 ("conditional risk"). This overview also shows that MediQ identified a large number of interactions that may increase the risk of bleeding in the studied surgical population and assigns them an "average" risk. The multidimensional ZHIAS evaluation additionally distinguishes a more relevant bleeding risk if NSAIDs are combined with the oral anticoagulant phenprocoumon from a lower risk when combined with low-dose heparins, and recognizes that low-dose aspirin combined with phenprocoumon may carry a substantial risk but that this is often a desired combination.

Dose adjustment in patients with impaired renal function

Creatinine measurements and corresponding MDRD-GFR estimations were available for 473 (92.9%) of all 509 included patients, and 65 patients (12.8%) had renal impairment with a GFR below 60 ml/min. Those patients had a total of 448 prescriptions for 61 distinct substances, which we analyzed for compliance with recommended dose adjustments. According to MediQ 26 substances accounting for 247 prescriptions in 58 patients require dose adjustment in case of impaired renal function, and we identified a failure to comply with recommended dose adjustment for 56 prescriptions in 44 patients. These are presented in **Table 7**, along with our assessment of 14 prescriptions having a major and 42 a minor risk of resulting in a related adverse event.

5. DISCUSSION

The current study used a customized interface with the CDSS MediQ for the retrospective identification of drug interactions and of substances that require dose adjustment for renal impairment in the discharge medication of surgical inpatients. MediQ was able to detect a very large number of (potential) drug interactions and therefore readily demonstrates the typical major strength as well as limitation of CDSS. Although this study was not designed to evaluate the sensitivity of MediQ to detect drug interactions, our results and the fact that its database contains about 2,000 substances and 20,000 detailed comments on related drug interactions suggests that MediQ is indeed a highly sensitive tool for the detection of interactions. On the other hand, our further evaluation based on ORCA and extended ZHIAS criteria concluded that only a minor fraction of alerts generated by MediQ is associated with a substantial risk that would require medication changes. This is of particular concern as such low specificity with regard to clinically relevant information is expected to compromise a physician's compliance to use such a system in daily practice [9-12]. In contrast, previous studies have shown that focused information that has been pre-selected by clinical pharmacologists and pharmacists and then clearly communicated to treating physicians does have a long-lasting reducing effect on the prescription of interacting drug combinations [5]. Our own experience from daily safety ward rounds at a university hospital are also in agreement with this finding, but in most clinical settings such resource intensive services are not routinely available. Furthermore, one-dimensional three level "traffic light" grading systems such as one used by MediQ do not necessarily correlate with clinical relevance of alerts [15, 18]. Therefore, filtering those alerts with high or average danger ratings does not reliably solve the issue of over-alerting. ORCA and ZHIAS consequently attempt a different approach, i.e. to focus on clinical management, and to record additional information in a categorical format. Although MediQ also contains additional information of high quality for clinical management in its free text comments, that information is easily overseen unless one

has the time to read those all. In contrast, based on its underlying categorical format ZHIAS can readily display that information in accordingly designed CDSS and therefore provides the basis to present it at first glance to the treating physician. For example, for the interaction between lisinopril and spironolactone (see Table 5) a CDSS using ZHIAS data could immediately direct the prescriber's attention to the current serum potassium value through one simple activated icon or even directly trigger retrieval of the latest measurement from the hospital's electronic patient information system. If potassium is indeed elevated a warning can be displayed with a high level of importance, whereas no further action besides monitoring (which could also be triggered through a ZHIAS-based system) would be required in case of a normal value. Furthermore, expert analysis of local results could help to put more emphasis on interactions that have frequently led to problems in the past in a specific setting or are otherwise of special interest. For example, recent data supports the view that not only "typical" NSAIDs but also metamizol can increase the risk of bleeding through inhibition of prostaglandin synthesis, which may be of special interest in a setting where this drug is frequently used as an analgesic after surgery [19, 20]. Finally, our finding that doses were apparently not adjusted for impaired renal function in 9% of all patients and in 68% of patients with a GFR <60 ml/min emphasizes that automated warnings for dose adjustment should also be part of integrated CPOE and CDSS.

Overall our results suggest that both, the integration of CDSS into the daily clinical prescription workflow as well as their design and content require major changes in order to effectively improve medication safety in real-life settings. First, interaction alerts must be automatically displayed at the time of prescription. Second, in order to avoid over-alerting by automated CDSS a paradigm shift may be necessary, away from CDSS with maximum sensitivity but instead towards CDSS with the best possible specificity for clinically relevant alerts. Third, we must therefore increase our efforts to define clinically relevant interactions and consider risk factors in order to implement that information into improved CDSS. The implementation of ZHIAS into CDSS is one possible solution that we explored in the current study. Additional studies will now be necessary in order to show whether accordingly

modified CDSS are able to actually modify prescribing behavior and reduce adverse drug events. However, we also conclude that any CDSS can only change prescribing behavior if its introduction is well coordinated and flanked by intense personal communication with local prescribers, further local customization and subsequent constant reevaluations. This process calls for a bridging function between theoretical pharmacological knowledge and clinical expertise, which can be a challenging new task for clinical pharmacologists. In our case, we discussed critical interactions and doses with the prescribing surgeons, and next we aim to introduce automated alerts at the time of prescriptions that are locally co-developed and supported by the department of surgery, followed by a systematic outcome evaluation.

CONCLUSIONS

This study used a new method for automated analysis of pharmacotherapy with CDSS and was therefore able to identify drug interactions in prescription data of a selected patient population with high efficiency. Results of such retrospective analyses can be used for the development of targeted measures to improve medication safety, directly where they have been identified in the past. Reclassification of the identified interactions according to a multidimensional operational interaction classification system suggests that only a minor fraction of all identified interactions involves a substantial risk. The implementation of such a classification into refined CDSS may reduce over-alerting and improve usability and therefore efficacy of CDSS to prevent adverse drug events in clinical practice. Future studies should investigate the impact of this approach on the prevention of adverse drug events in clinical practice.

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7. TABLES

Table 1 Characteristics of the study patients (N=509)

Characteristics	n	%
Sex		
Female	280	55.0
Male	229	45.0
Age category (years)		
<25	20	3.9
25-44	46	9.0
45-64	138	27.1
65-84	243	47.7
85 and older	62	12.2
Primary admission diagnosis[1]		
Trauma	209	41.1
Visceral surgery	121	23.8
Orthopedics	101	19.8
Urology	22	4.3
Other	56	11.0
Admission		
Elective	196	38.5
Emergency	313	61.5
Duration of hospitalization (nights)		
4-6	173	34.0
7-10	152	29.9
11-30	172	33.8
>30	12	2.4
Renal function (MDRD-GFR, ml/min/1.73 m^2)[2]		
≥60	408	80.2
30-59	61	12.0
<30 or dialysis	4	0.8
Unknown	36	7.1
Number of concomitant drugs (polypharmacy)		
2-4	250	49.1
5-8	173	34.0
≥9	86	16.9

[1]Only one primary diagnosis per patient; [2]Last measurement before discharge

Table 2 Discharge medication of the study population

Drugs	n prescriptions		n patients with prescriptions	
	n	%	n	%
Total	**2,729**	**100**	**509**	**100**
NSAIDs including paracetamol and metamizol[1]	712	26.1	446	87.6
Antithrombotics[1]	447	16.4	316	62.1
RAA system inhibitors and diuretics	280	10.3	178	35.0
Other cardiovascular agents	249	9.1	168	33.0
Gastrointestinal agents	228	8.4	204	40.1
Anti-infective agents	143	5.2	109	21.4
Dietary supplements	123	4.5	76	14.9
Opioids	82	3.0	74	14.5
Antidepressants	79	2.9	63	12.4
Antidiabetic agents	78	2.9	51	10.0
Other nervous system agents	53	1.9	44	8.6
Anxiolytics, sedatives and hypnotics	49	1.8	43	8.4
Antipsychotics	47	1.7	40	7.9
Hormones	45	1.6	41	8.1
Respiratory tract agents	37	1.4	24	4.7
Anticonvulsants	28	1.0	24	4.7
Antineoplastic and immunological agents	7	0.3	7	1.4
Other	42	1.5	39	7.7

[1] Including low dose acetylsalicylic acid, which is *not* included among NSAIDs

Table 3 Identification and grading of interactions by MediQ and subsequent reclassification based on ORCA criteria for MediQ level 2 and 3 alerts as part of the ZHIAS classification

Drug interaction classifications	Frequency of distinct combinations in 509 studied patients		Frequency of combined prescriptions in 509 studied patients	
	n	%	n	%
MediQ level 3 ("high")	**5**	**100**	**10**	**100**
ORCA level 1 ("contraindicated")	0	0	0	0
ORCA level 2 ("provisionally contraindicated")	1	20.0	1	10.0
ORCA level 3 ("conditional risk")	3	60.0	8	80.0
ORCA level 4 ("minimal risk")	1	20.0	1	10.0
MediQ level 2 ("average")	**149**	**100**	**551**	**100**
ORCA level 1 ("contraindicated")	9	6.0	10	1.8
ORCA level 2 ("provisionally contraindicated")	10	6.7	76	13.8
ORCA level 3 ("conditional risk")	94	63.1	302	54.8
ORCA level 4 ("minimal risk")	36	24.2	163	29.6
MediQ level 1 ("low")	**529**	**100**	**1,997**	**100**
MediQ level 0 ("no interaction")	**499**	**100**	**1,849**	**100**

Table 4 ZHIAS reclassification by ORCA categories of all 561[1] interactions classified by MediQ as high or average danger and their corresponding frequencies in the study population.

ZHIAS classification	Frequencies in 509 patients, stratified over ORCA classes					
	ORCA 1 (contraindicated / risk outweighs benefit)		ORCA 2 (provisionally contraindicated)		ORCA 3 (conditional risk)	
	n	%	n	%	n	%
TOTAL combinations	**10**	**100**	**77**	**100**	**310**	**100**
Management						
Desired	0	0	22	28.6	68	21.9
Consider alternative	10	100	55	71.4	247	79.7
Monitoring	0	0	77	100	263	84.8
Mechanism[2]						
Pharmacokinetic	0	0	6	7.8	56	18.1
Pharmacodynamic	10	100	74	96.1	275	88.7
Adverse events with increased risk resulting from interactions[3]						
Increased drug effect	8	80.0	75	97.4	216	69.7
Decreased drug effect	1	10.0	1	1.3	46	14.8
Sedation (CNS)	4	40.0	5	6.5	17	5.5
Serotonin syndrome	1	10.0	1	1.3	21	6.8
Extrapyramidal symptoms	0	0	1	1.3	1	0.3
Seizures	2	20.0	1	1.3	17	5.5
CNS effects other	3	30.0	2	2.6	6	1.9
Nephrotoxicity	3	30.0	1	1.3	37	11.9
Hepatotoxicity	0	0	0	0	4	1.3
QTc prolongation	0	0	2	2.6	17	5.5
Cardiac arrhythmias	0	0	3	3.9	27	8.7
Thrombosis	0	0	0	0	6	1.9
Bleeding	4	40.0	70	90.9	171	55.2
Blood pressure up	0	0	0	0	34	11.0
Blood pressure down	1	10.0	3	3.9	22	7.1
Cardiovascular effects other	0	0	0	0	11	3.5
Hyperkalemia	1	10.0	0	0	39	12.6
Hypokalemia	0	0	0	0	9	2.9
Hyponatremia	0	0	1	1.3	5	1.6
Metabolic/endocrine effects	0	0	1	1.3	1	0.3
Gastrointestinal toxicity	2	20.0	1	1.3	8	2.6
Blood glucose up	0	0	1	1.3	2	0.6
Blood glucose down	0	0	0	0	2	0.6
Muscular toxicity	0	0	1	1.3	7	2.3
Allergy	0	0	0	0	4	1.3
Other	0	0	0	0	8	2.6

[1] Another 164 interactions classified by MediQ as high or average danger were reclassified into ORCA 4 = minimal risk (see Table 3) and are not shown in detail in this table.

[2] PK and PD mechanisms can be involved concomitantly and combined total may therefore exceed 100%

[3] Several adverse events may result from one combination and combined total may therefore exceed 100%

Table 5 Presentation of all specific interactions with the highest severity rating according to MediQ ("high danger") and/or ZHIAS (ORCA 1, "contraindicated / risk always outweighs benefit")

Drug combination	Frequency in 509 patients		MediQ danger rating	ZHIAS classification		
				ORCA[1]	Management[2]	Adverse event with increased risk
	n	%				
Lisinopril - spironolactone	5	1.0	High	3	A / M	Hyperkalemia
Atorvastatin - amiodarone	2	0.4	High	3	A / M	Muscle toxicity
Paroxetine - metoprolol	1	0.2	High	2	A / M	Hypotension, bradycardia
Salmeterol - amiodarone	1	0.2	High	3	M	QTc, arrhythmias
Melitracen - amiodarone	1	0.2	High	4	M	QTc, arrhythmias
Tramadol - oxycodone	2	0.4	Average	1	A	Sedation, seizures
Tramadol - buprenorphine	1	0.2	Average	1	A	Sedation, seizures
Tramadol - codeine	1	0.2	Average	1	A	Sedation, seizures
Tramadol - fentanyl	1	0.2	Average	1	A	Sedation, seizures, serotonin syndrome
Lisinopril - irbesartan	1	0.2	Average	1	A	Hyperkalemia, renal deterioration
Ginkgo biloba - phenprocoumon	1	0.2	Average	1	A	Bleeding
Ginkgo biloba - clopidogrel	1	0.2	Average	1	A	Bleeding
Mefenamic acid - diclofenac	1	0.2	Average	1	A	GI bleeding
Mefenamic acid - ibuprofen	1	0.2	Average	1	A	GI bleeding

[1] ORCA notation: 1 – contraindicated, 2 – provisionally contraindicated, 3 – conditional risk.

[2] D = desired interaction; A = consider an available alternative; M = special monitoring recommended

Table 6 Presentation of all specific drug interactions classified by ZHIAS as ORCA 2 ("provisionally contraindicated"), and the 10 most frequent classified as ORCA 3 ("conditional risk") in 509 analyzed patients.

Combination name	Frequency in 509 patients		MediQ danger rating	ORCA[1]	Management[2]	Adverse event with increased risk
	n	%				
All combinations classified as "provisionally contraindicated" by ZHIAS						
Mefenamic acid - phenprocoumon	48	9.4	Average	2	A / M	Bleeding
Low dose acetylsalicylic acid - phenprocoumon	20	3.9	Average	2	D / M	Bleeding
Any two benzodiazepines	2	0.4	Average	2	D / M	Sedation
Metoprolol - paroxetine	1	0.2	High	2	A / M	Bradycardia, hypotension
Amiodarone - nebivolol	1	0.2	Average	2	A / M	Bradycardia, hypotension
Fluoxetine - citalopram	1	0.2	Average	2	A / M	Hyponatremia, serotonin syndrome
Ginkgo biloba - mefenamic acid	1	0.2	Average	2	A / M	Bleeding
Lithium - mefenamic acid	1	0.2	Average	2	A / M	Lithium intoxication
Quetiapine - primidone	1	0.2	Average	2	A / M	Sedation, loss of quetiapine efficacy
Valproic acid - phenobarbital	1	0.2	Average	2	A / M	Sedation, other CNS
10 most frequent combinations classified as "conditional risk" by ZHIAS						
Mefenamic acid - dalteparin	69	13.6	Average	3	A / M	Bleeding
Low dose acetylsalicylic acid - dalteparin	31	6.1	Average	3	D / M	Bleeding
Metamizol - phenprocoumon	28	5.5	Average	3	A / M	Bleeding
Mefenamic acid - metamizol	12	2.4	Average	3	D / M	Bleeding
Mefenamic acid - lisinopril	10	2.0	Average	3	A / M	Hypertension, nephrotoxicity
Diclofenac - dalteparin	8	1.6	Average	3	A / M	Bleeding
Tramadol - citalopram/ escitalopram	6	1.2	Average	3	A / M	Serotonin syndrome
Allopurinol - amoxicillin	4	0.8	Average	3	A / M	Exanthema, skin rashes
Allopurinol - phenprocoumon	4	0.8	Average	3	M	Bleeding
Tramadol - quetiapine	4	0.8	Average	3	A / M	Sedation, seizures

[1] ORCA notation: 1 – contraindicated, 2 – provisionally contraindicated, 3 – conditional risk.

[2] D = desired interaction; A = consider an available alternative; M = special monitoring recommended

Table 7 Prescriptions without recommended dose adjustment for impaired renal function

Drug	n prescriptions w/o adjustment	GFR range (ml/min)	Recomm. max. dose (mg/day)	Actual dose range (mg/day)	Risk of related adverse event
Metformin	8	30-59	850	1,000-1,700	Major
Diclofenac	2	39-57	75	100-150	Major[1]
Metamizol	2	29-30	Avoid high doses	4,000	Major[1]
Perindopril	1	48	2	8	Major[1]
Rosuvastatin	1	25	Avoid	10	Major
Paracetamol	39	25-59	2,500	4,000	Minor
Atenolol	1	32	50	75	Minor
Hydrochlorothiazide	1	29	Avoid	12.5	Minor
Pregabalin	1	51	300	375	Minor

[1] The combination of NSAIDs, ACE-inhibitors and preexisting renal impairment is an important risk factor for acute renal failure, particularly if doses are not adjusted.

8. FIGURES

Fig. 1 Overview of study procedures and global results

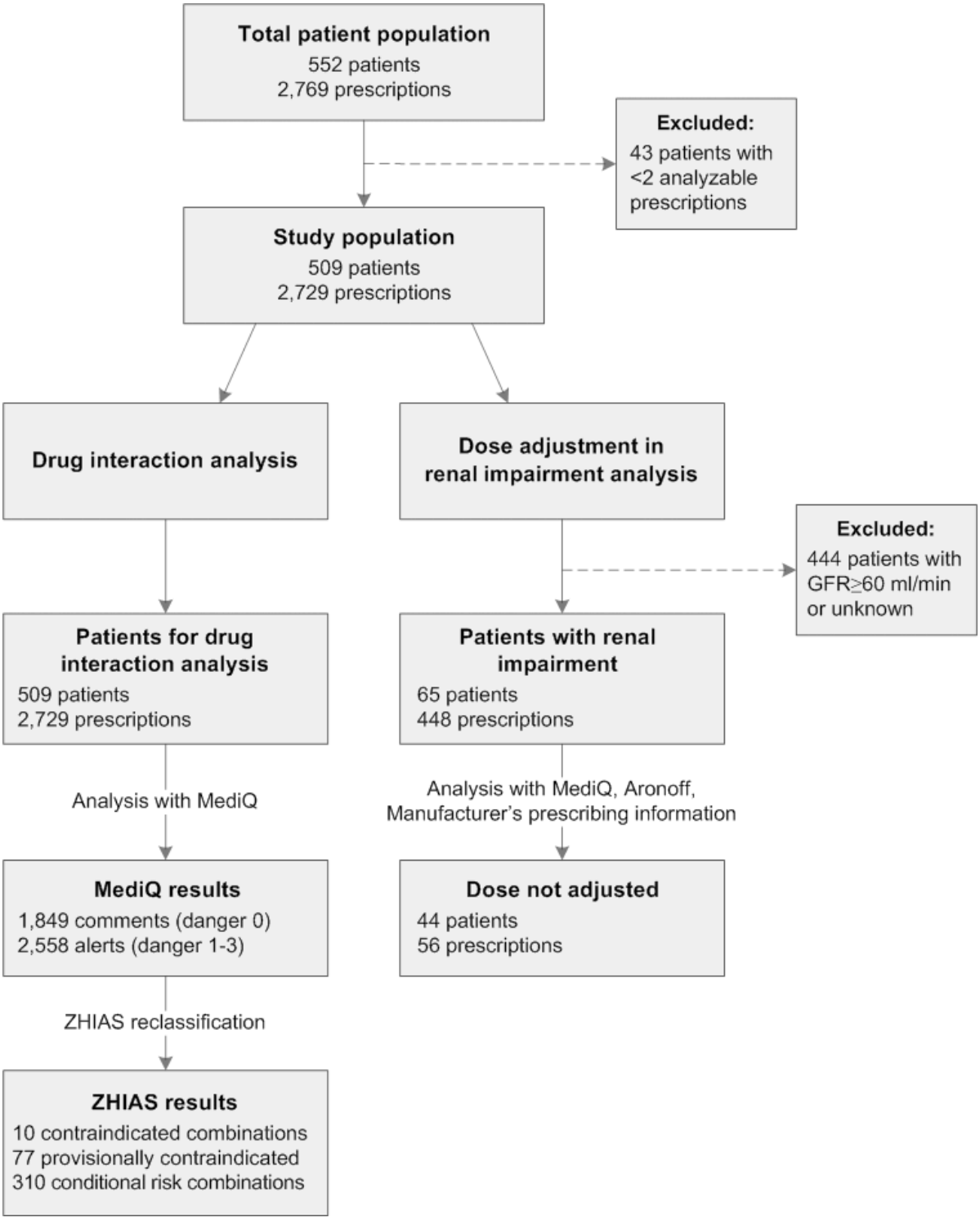
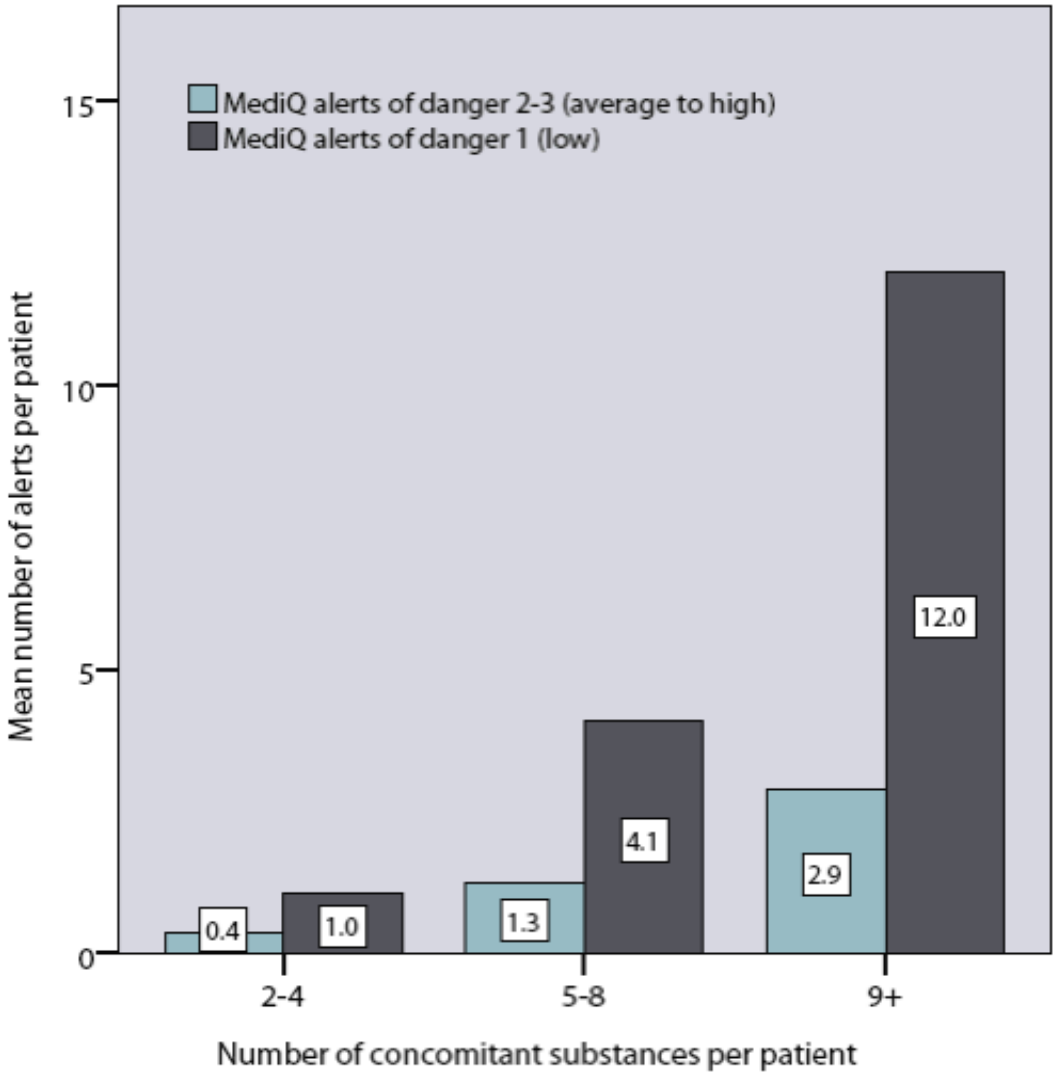


Fig. 2 Correlation between polypharmacy and identification of interactions by different danger categories for interactions according to MediQ



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10. Curriculum Vitae

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